

**Remarks:**

Applicant submits these amendments with a Request for Continued Examination in view of the Advisory Action mailed February 22, 2006, in which the Examiner stated that entry of the after final amendments filed January 26, 2006, did not place the application in condition for allowance. Applicants previously filed an Amendment and Notice of Appeal on January 26, 2006, in response to a final Office Action dated October 26, 2005. Applicant respectfully requests entry of these amendments and that the previously-filed amendments dated January 26, 2006, not be entered.

After entry of the amendment, claims 3-6, 11, 16-24, 29, 35-39, 44, 48, 50, 55, 59, 61, 66-70, 72-76, 80-82, and 91 are pending.

Claims 1, 2, 7-10, 12-15, 25-28, 30-33, 40-43, 45-47, 51-54, 56-58, 62-65, 77-79, 84-87, 89, 90 and 92 have been cancelled without prejudice or disclaimer. Applicant retains the right to pursue the subject matter of these claims in future continuation or divisional applications.

Claim 3 has been editorially amended and is supported by original claim 1.

Claims 6, 24, 39, 50 and 61 have been amended and are supported by original claims 9, 27, 42, 53 and 64 respectively.

Claims 16, 19, 20, 21-23 have been amended and are supported by original claim 15. In view thereof, claim 15 has been cancelled and the dependency of claims 16, 19, 20, 21, 23 and 24 have been amended.

Claims 35 and 36 have been amended and are supported by original claim 33. In view thereof claim 33 has been cancelled and the dependency of claims 35, 36 and 39 have been amended.

The dependency of claims 48 and 59 has been corrected.

Claim 76 has been amended. In view thereof claim 77 has been cancelled.

The dependency of claim 81 has been corrected.

Claim 87 has been editorially amended.

Claim 91 has been amended and is supported by original claims 33 and 35.

No issues of new matter should arise and entry of the amendment is respectfully requested.

**A. Rejection under 35 U.S.C. §112, First Paragraph**

Claims 6-73 and 76-92 are rejected under 35 USC § 112, first paragraph, as lacking enablement.

Applicant respectfully traverses the rejection and respectfully submits that the claims satisfy the requirement under 35 U.S.C. § 112, first paragraph.

As pointed out by the Examiner on page 2 of the Office Action, the specification is enabled for the treatment of hypertension using the compounds of Formula I, IV and V. In view thereof, and in order to further prosecution, claims 6, 24, 39, 50 and 61 have been amended to recite the treatment of hypertension. Method claims 7-10, 12-14, 25-28, 30-33, 40-43, 45-47, 51-54, 56-58, 62-65, 78, 79, 84-87 and 89 have been cancelled.

In view of the above, Applicant respectfully submits that the claims satisfy the requirement under 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection under this provision be withdrawn.

**B. Rejection under 37 C.F.R. §112, second paragraph**

Claims 1, 2, 6, 7, 15, 19, 24, 25, 33, 34, 39, 40, 48, 50, 51, 59, 61, 62, 76, 78, 79, 80, 84, 87 and 90-92 are rejected under 37 C.F.R. §112, second paragraph, as being indefinite.

The rejections are addressed in the order in which they appear in the Office Action.

Applicant respectfully traverses the rejection and respectfully submit that the claims satisfy the requirement under 35 U.S.C. § 112, first paragraph.

In order to further prosecution, claims 1 and 2 have been cancelled.

As mentioned above, the discussion of which is incorporated herein in its entirety, claims 6, 24, 39, 50, and 61 have been amended.

Claims 15, 90 and 92 have been cancelled. Claim 76 has been amended to delete "at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase".

Claim 19 has been amended. The specific compounds comprising (i) at least one ON-O-, ON-N- or ON-C- group; or (ii) at least one O<sub>2</sub>N-O-, O<sub>2</sub>N-N-, O<sub>2</sub>N-S- or -O<sub>2</sub>N-C- group are defined in claims 20 and 21 respectively.

Claim 33 has been cancelled. The specific antioxidants are defined in claims 35 and 36.

Claim 91 has been amended to define the specific antioxidants.

Claim 48 has been amended. Applicant respectfully submits that one skilled in the art would readily know what specific compounds are included in these well known classes of cardiovascular compounds. Additionally the specific compounds included in these well known classes of cardiovascular compounds are defined in the specification, at, for example, page 48, line 14 to page 49, line 32.

Claims 59 and 91 were previously modified to define the cardiovascular compounds as “a angiotensin-converting enzyme inhibitor, beta-adrenergic blocker, cholesterol reducer, calcium channel blocker, angiotensin II receptor antagonist, endothelin antagonist, renin inhibitor”. One skilled in the art would readily know recognize these classes of well known cardiovascular compounds and would know which specific compounds are included in these classes of well known cardiovascular compounds. Additionally the specific compounds included in these well known classes of cardiovascular compounds are defined in the specification, at, for example, page 48, line 14 to page 49, line 32.

Claims 78 and 79 have been cancelled in order to further prosecution.

In view of the above, Applicant respectfully submits that the claims satisfy the requirement under 35 U. S. C. §112, second paragraph, and respectfully request that the rejections under this provision be withdrawn.

**C. Rejection under 35 U.S.C. §103**

Claims 1-92 are rejected under 35 U.S.C. § 103(a) as obvious over Van Lommen et al. (U.S. Patent No. 4,654,362), in view of Loscalzo et al. (U.S. Patent No. 6,635,273).

As previously pointed out by the Examiner, Van Lommen does not disclose or suggest the presently claimed nebivolol compounds that comprise at least one NO and/or NO<sub>2</sub> group, and does not provide any motivation or incentive to add at least one NO and/or NO<sub>2</sub> group to nebivolol.

Loscalzo teaches methods of treating vascular diseases due to nitric oxide insufficiency by administration of a nitrosated beta-adrenergic blocker. Nebivolol is listed in the laundry list of possible beta-adrenergic blocker that can be administered. Loscalzo does not disclose the presently claimed nitrosated and/or nitrosylated nebivolol compounds of Formula (I), (IV) or (V), nor does Loscalzo suggest or motivate one to make the nitrosated and/or nitrosylated nebivolol compounds of Formula (I), (IV) or (V) of the present invention. As pointed out by the Examiner from Loscalzo, it is not clear how to attach the –NO group or the –NO<sub>2</sub> group to the

structure of nebivolol. There is absolutely no guidance in Loscalzo as to how to attach the –NO group or the –NO<sub>2</sub> group to nebivolol, where it is attached to nebivolol and how many –NO group or the –NO<sub>2</sub> group are attached to nebivolol. Hence Loscalzo taken alone does not render the claimed invention obvious. Additionally Loscalzo does not provide any motivation or suggestion to modify Van Lommen to arrive at the claimed invention. In view thereof, Loscalzo in combination with Van Lommen does not motivate one to arrive at the present invention.

In view thereof, Applicant respectfully submits that the claims of the present invention are unobvious over the cited references, alone and in combination, and respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

**D. Conclusion**

Applicant respectfully requests reconsideration and allowance of claims 3-6, 11, 16-24, 29, 35-39, 44, 48, 50, 55, 59, 61, 66-70, 72-76, 80-82, and 91. The Examiner is encouraged to contact the undersigned concerning any questions about the present application.

Respectfully submitted,



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